Amendments To The Specification

Please amend the paragraph beginning at page 9, line 2, as follows:

Two patients in whom we noted rapid reduction of blood tumor cells, which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia, were studies. Also, two additional patients were collected from physician-submitted reports of adverse events related to RITUXAN® treatment. Pretreatment characterization of these patients included a median age of 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), or transformed non-Hodgkin's lymphoma. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All four patients developed a unique syndrome of severe infusion-related reactions characterized by fever, rigors, bronchospasm with associated hypoxemia, requiring temporary cessation of RITUXAN® therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pretreatment 98 x 10^9 per L; range 73-132 vs. mean post-treatment 11 x 10^9 per L; range 3.7-24.6) with mild electrolyte evidence of rapid tumor lysis. Thrombocytopenia, a finding not commonly associated with RITUXAN® therapy was noted in all four patients (mean pretreatment platelet counts 145 x 10^9 per L; range 57-277 vs. mean post-treatment 56 x 10^9/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent RITUXAN® treatment were well tolerated in all patients. Two subsequent patients with CLL have been treated with high blood tumor counts utilizing stepped-up dosing (100 ~~mg~~ mg/m^2 day 1 followed by rest of therapy on day 2) with demonstrated efficacy, thrombocytopenia but minimal infusion-related toxicity. RITUXAN® administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thromocytopenia mandating careful clinical monitoring. Given the preliminary activity of RITUXAN® in these patients, future studies in CLL and PLL, utilizing a stepped-up dosing schedule, is to be conducted.

Please amend the paragraph beginning at page 12, line 7, as follows:

RITUXAN® is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 ~~mg/m^3~~ mg/m^2 weekly/four response rate in relapsed patients (PTS) was 43% (~~McClaughlin et al, KOO, Vol.~~

~~14, 1988~~ McLaughlin et al. (1998) *J Clin Oncol* 16(8):2825-33). Patients with small lymphocytic lymphoma had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN®. Reduced response seen in SLL could be related to lower density of CD20 antigen and/or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL. In an attempt to maximize activities in CLL we are conducting a Phase I/II study. All patients receive a first dose of 375 ~~mg/m^3~~ mg/m^2 to minimize infusion-relapsed side effects. Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 ~~mg/m^3~~ mg/m^2. Medium age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Medium white blood cell count was 40 x 10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10^9/L (range, 16-160), median β_2 immunoglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 ~~mgm^3~~ mg/m^2); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 ~~mg/m^3~~ mg/m^2 dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 ~~mg/m^3~~ mg/m^2, 3 at 650 ~~mg/m^3~~ mg/m^2, 1 at 825 ~~mg/m^3~~ mg/m^2). One patient treated at 650 ~~mg/m^3~~ mg/m^2 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.